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to PHARMASEARCH
NEWS 3 Oct 09 Korean abstracts now included in Derwent World Patents
Index
NEWS 4 Oct 09 Number of Derwent World Patents Index updates increased
NEWS 5 Oct 15 Calculated properties now in the REGISTRY/ZREGISTRY File
NEWS 6 Oct 22 Over 1 million reactions added to CASREACT
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NEWS 13 Nov 30 Files VETU and VETB to have open access
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NEWS 15 Dec 10 DGENE BLAST Homology Search
NEWS 16 Dec 17 WELDASEARCH now available on STN
NEWS 17 Dec 17 STANDARDS now available on STN
NEWS 18 Dec 17 New fields for DPCI
NEWS 19 Dec 19 CAS Roles modified
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NEWS 21 Jan 25 BLAST(R) searching in REGISTRY available in STN on the Web
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NEWS 23 Jan 29 FSTA has been reloaded and moves to weekly updates
NEWS 24 Feb 01 DKILIT now produced by FIZ Karlsruhe and has a new update
frequency
NEWS 25 Feb 19 Access via Tymnet and SprintNet Eliminated Effective 3/31/02

NEWS EXPRESS February 1 CURRENT WINDOWS VERSION IS V6.0d,
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FILE 'MEDLINE' ENTERED AT 14:24:01 ON 01 MAR 2002

=>
=> s polymeric (w) prodrug
L1 255 POLYMERIC (W) PRODRUG

=> s Met-Nle
L2 100 MET-NLE

=> s 1 and 2
L3 7589691 1 AND 2

=>

=> s l1 and l2
L4 0 L1 AND L2

=> s Met-beta-Ala
L5 9 MET-BETA-ALA

=> s l1 and l5
L6 0 L1 AND L5

=> s Gln-Gly
L7 1227 GLN-GLY

=> s l1 and l7
L8 0 L1 AND L7

=> s Asp-Pro
L9 1504 ASP-PRO

=> s l1 and l9
L10 0 L1 AND L9

=> s dipeptide linking arm
L11 0 DIPEPTIDE LINKING ARM

=> s dipeptide
L12 37490 DIPEPTIDE

=> s l1 and l12
L13 3 L1 AND L12

=> d ibib abs l13 1-3

L13 ANSWER 1 OF 3 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2001:227708 BIOSIS

DOCUMENT NUMBER: PREV200100227708

TITLE: **Polymeric prodrug** for release of an
antitumoral agent by specific enzymes.

AUTHOR(S): Cavallaro, Gennara; Pitarresi, Giovanna; Licciardi,
Mariano; Giammona, Gaetano (1)

CORPORATE SOURCE: (1) Dipartimento di Chimica e Tecnologie Farmaceutiche, Via
Archirafi 32, 90123, Palermo: gaegiamm@unipa.it Italy

SOURCE: Bioconjugate Chemistry, (March April, 2001) Vol. 12, No. 2,
pp. 143-151. print.
ISSN: 1043-1802.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The clinical usefulness of antitumor chemotherapy has been strongly limited by the lack of specificity of most anticancer drugs, which act also against healthy cells. The aim of this work was to design, synthesize, and evaluate a macromolecular prodrug of Cytarabine, a known antitumor drug, which is a specific substrate for plasmin enzyme whose concentration is high in various kinds of tumor mass as a result of plasminogen activator secretion. α , β -Poly(N-hydroxyethyl)-DL-aspartamide (PHEA), a known synthetic and biocompatible polyamino acid, was used as a drug carrier, and Cytarabine was linked to PHEA by D-Val-Leu-Lys spacer synthesized beginning from Cbz-D-Val-LeuOH dipeptide and N⁶-CbzLys methyl ester. The content of Cytarabine in the purified PHEA-D-Val-Leu-Lys-Cytarabine conjugate was equal to 3% w/w. In vitro experiments in the presence of plasmin evidenced the ability of this enzyme to strongly increase drug release from the macromolecular prodrug, as well as plasma incubation shows high stability of drug-polymer linkage. The direct linkage of Cytarabine to PHEA was also performed and, like PHEA-D-Val-Leu-Lys-Cytarabine conjugate, the obtained PHEA-Cytarabine conjugate showed high stability in plasma, but no release of Cytarabine was revealed in the presence of plasmin.

L13 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:156311 CAPLUS
DOCUMENT NUMBER: 134:344484
TITLE: **Polymeric Prodrug** for Release of
an Antitumoral Agent by Specific Enzymes
AUTHOR(S): Cavallaro, Gennara; Pitarresi, Giovanna; Licciardi,
Mariano; Giammona, Gaetano
CORPORATE SOURCE: Dipartimento di Chimica e Tecnologie Farmaceutiche,
Palermo, 90123, Italy
SOURCE: Bioconjugate Chem. (2001), 12(2), 143-151
CODEN: BCCHEs; ISSN: 1043-1802
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The clin. usefulness of antitumor chemotherapy has been strongly limited by the lack of specificity of most anticancer drugs, which act also against healthy cells. The aim of this work was to design, synthesize, and evaluate a macromol. prodrug of cytarabine, a known antitumor drug, which is a specific substrate for plasmin enzyme whose concn. is high in various kinds of tumor mass as a result of plasminogen activator secretion. α , β -Poly(N-hydroxyethyl)-DL-aspartamide (PHEA), a known synthetic and biocompatible polyamino acid, was used as a drug carrier, and Cytarabine was linked to PHEA by D-Val-Leu-Lys spacer synthesized beginning from Cbz-D-Val-LeuOH dipeptide and N⁶-CbzLys Me ester. The content of Cytarabine in the purified PHEA-D-Val-Leu-Lys-cytarabine conjugate was equal to 3% wt./wt. In vitro expts. in the presence of plasmin evidenced the ability of this enzyme to strongly increase drug release from the macromol. prodrug, as well as plasma incubation shows high stability of drug-polymer linkage. The direct linkage of cytarabine to PHEA was also performed and, like PHEA-D-Val-Leu-Lys-cytarabine conjugate, the obtained PHEA-cytarabine conjugate showed high stability in plasma, but no release of cytarabine was revealed in the presence of plasmin.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 3 MEDLINE

ACCESSION NUMBER: 2001459729 MEDLINE
DOCUMENT NUMBER: 21213485 PubMed ID: 11312674
TITLE: **Polymeric prodrug** for release of an
antitumoral agent by specific enzymes.
AUTHOR: Cavallaro G; Pitarresi G; Licciardi M; Giammona G
CORPORATE SOURCE: Dipartimento di Chimica e Tecnologie Farmaceutiche, Via
Archirafi 32, 90123 Palermo, Italia.
SOURCE: BIOCONJUGATE CHEMISTRY, (2001 Mar-Apr) 12 (2) 143-51.
Journal code: A1T; 9010319. ISSN: 1043-1802.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010820
 Last Updated on STN: 20010820
 Entered Medline: 20010816

AB The clinical usefulness of antitumor chemotherapy has been strongly limited by the lack of specificity of most anticancer drugs, which act also against healthy cells. The aim of this work was to design, synthesize, and evaluate a macromolecular prodrug of Cytarabine, a known antitumor drug, which is a specific substrate for plasmin enzyme whose concentration is high in various kinds of tumor mass as a result of plasminogen activator secretion. alpha,beta-Poly(N-hydroxyethyl)-DL-aspartamide (PHEA), a known synthetic and biocompatible polyamino acid, was used as a drug carrier, and Cytarabine was linked to PHEA by D-Val-Leu-Lys spacer synthesized beginning from Cbz-D-Val-LeuOH **dipeptide** and N6-CbzLys methyl ester. The content of Cytarabine in the purified PHEA-D-Val-Leu-Lys-Cytarabine conjugate was equal to 3% w/w. In vitro experiments in the presence of plasmin evidenced the ability of this enzyme to strongly increase drug release from the macromolecular prodrug, as well as plasma incubation shows high stability of drug-polymer linkage. The direct linkage of Cytarabine to PHEA was also performed and, like PHEA-D-Val-Leu-Lys-Cytarabine conjugate, the obtained PHEA-Cytarabine conjugate showed high stability in plasma, but no release of Cytarabine was revealed in the presence of plasmin.

=> d his

(FILE 'HOME' ENTERED AT 14:22:14 ON 01 MAR 2002)

FILE 'BIOSIS, CAPLUS, MEDLINE' ENTERED AT 14:24:01 ON 01 MAR 2002

L1 255 S POLYMERIC (W) PRODRUG
L2 100 S MET-NLE
L3 7589691 S 1 AND 2
L4 0 S L1 AND L2
L5 9 S MET-BETA-ALA
L6 0 S L1 AND L5
L7 1227 S GLN-GLY
L8 0 S L1 AND L7
L9 1504 S ASP-PRO
L10 0 S L1 AND L9
L11 0 S DIPEPTIDE LINKING ARM
L12 37490 S DIPEPTIDE
L13 3 S L1 AND L12

=> s polymeric (w) drug (w) conjugate

L14 17 POLYMERIC (W) DRUG (W) CONJUGATE

=> s dipeptide

L15 37490 DIPEPTIDE

=> s l14 and l15

L16 0 L14 AND L15

=> s drug (w) polymer (w) derivatives

L17 1 DRUG (W) POLYMER (W) DERIVATIVES

=> d l17

L17 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
AN 1991:566605 CAPLUS
DN 115:166605
TI Biologically active **drug polymer derivatives**
IN Veronese, Francesco; Sartore, Luciana; Orsolini, Piero; Deghenghi, Romano
PA Debiopharm S. A., Switz.
SO PCT Int. Appl., 22 pp.
 CODEN: PIXXD2
DT Patent
LA English

FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------|---|------|----------|-----------------|----------|
| PI | WO 9101758 | A1 | 19910221 | WO 1990-EP1261 | 19900726 |
| | W: CA, JP, US | | | | |
| | RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE | | | | |
| | CA 2038935 | AA | 19910208 | CA 1990-2038935 | 19900726 |
| | CA 2038935 | C | 19981208 | | |
| | EP 437563 | A1 | 19910724 | EP 1990-910711 | 19900726 |
| | EP 437563 | B1 | 19950222 | | |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE | | | | |
| | JP 04501121 | T2 | 19920227 | JP 1990-510696 | 19900726 |
| | ES 2069082 | T3 | 19950501 | ES 1990-910711 | 19900726 |
| | US 5286637 | A | 19940215 | US 1993-1434 | 19930107 |
| PRAI | GB 1989-18009 | | 19890807 | | |
| | GB 1989-19618 | | 19890830 | | |
| | WO 1990-EP1261 | | 19900726 | | |
| | US 1991-681493 | | 19910603 | | |

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=> d ibib abs l17

L17 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1991:566605 CAPLUS

DOCUMENT NUMBER: 115:166605

TITLE: Biologically active drug polymer
derivatives

INVENTOR(S): Veronese, Francesco; Sartore, Luciana; Orsolini,
Piero; Deghenghi, Romano

PATENT ASSIGNEE(S): Debiopharm S. A., Switz.

SOURCE: PCT Int. Appl., 22 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|---|------|----------|-----------------|----------|
| | WO 9101758 | A1 | 19910221 | WO 1990-EP1261 | 19900726 |
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| | CA 2038935 | AA | 19910208 | CA 1990-2038935 | 19900726 |
| | CA 2038935 | C | 19981208 | | |
| | EP 437563 | A1 | 19910724 | EP 1990-910711 | 19900726 |
| | EP 437563 | B1 | 19950222 | | |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE | | | | |
| | JP 04501121 | T2 | 19920227 | JP 1990-510696 | 19900726 |
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| | US 5286637 | A | 19940215 | US 1993-1434 | 19930107 |
| PRIORITY APPLN. INFO.: | | | | GB 1989-18009 | 19890807 |
| | | | | GB 1989-19618 | 19890830 |
| | | | | WO 1990-EP1261 | 19900726 |
| | | | | US 1991-681493 | 19910603 |

AB Biol. active protein derivs. useful as medicaments comprise
RO(CH₂CH₂O)_n(CO)NHX(CO) (R = lower alkyl; n = 25-250; X when combined with
the adjacent NH and CO groups represents amino acid, dipeptide or
tripeptide residue; Z when combined with the adjacent NH group represents
a peptide, protein, NH- or NH₂-contg. drug residue). A method for prepg.
the protein derivs. are detailed. Monomethoxypolyethylene glycol glycine
succinimidyl ester (prepn. given) was reacted with superoxide dismutase.
The product was dried at low temp. under vacuum, dissolved, and concd.
The product was stable after 6 such cycles while the unmodified enzyme

lost .gtoreq.15% of its activity under the same conditions

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FILE 'BIOSIS, CAPLUS, MEDLINE' ENTERED AT 14:24:01 ON 01 MAR 2002

| | | | |
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| L7 | 1227 | S | GLN-GLY |
| L8 | 0 | S | L1 AND L7 |
| L9 | 1504 | S | ASP-PRO |
| L10 | 0 | S | L1 AND L9 |
| L11 | 0 | S | DIPEPTIDE LINKING ARM |
| L12 | 37490 | S | DIPEPTIDE |
| L13 | 3 | S | L1 AND L12 |
| L14 | 17 | S | POLYMERIC (W) DRUG (W) CONJUGATE |
| L15 | 37490 | S | DIPEPTIDE |
| L16 | 0 | S | L14 AND L15 |
| L17 | 1 | S | DRUG (W) POLYMER (W) DERIVATIVES |